

enclosed herewith to complete the record of this application. Applicants have amended the specification on page 1 and will file a substitute declaration and power of attorney.

Accordingly, it is believed that Applicants are entitled to a priority date of January 23, 1996.

35 USC 112

In view of the amendments made above, rejection of Claims 1-12 and 15-17 under 35 USC 112, first paragraph is believed to be unsustainable and should be withdrawn. The claims have been amended to use enabling language suggested by the Examiner.

Antibodies MHM23 and H52 bind to the extracellular domain of CD18 and inhibit or reduce CD18 biological properties in a preferred embodiment of the invention. Page 8, lines 18-25 and the example on pages 26-29 demonstrates an antibody which binds to an extracellular domain of CD18 and inhibits or reduces CD18 biological activity.

35 USC 102(f)

During the discussion noted above, Applicants' representative discussed a Petition to Correct Inventorship adding the name of Cordell Gross as an inventor in priority application USSN 08/589,982. A copy of this Petition was present in the official file and reviewed with the Examiner. In view of the Petition to Correct Inventorship in the priority application, the inventorship of the priority application and the present application is identical. Applicants have not yet received a decision on this petition. In view of the foregoing, the rejection of Claims 1-12 and 15-17 under 35 USC 102(f) is believed to be unsustainable and should be withdrawn.

35 USC 103


The pending claims are not disclosed nor rendered obvious by the combined disclosures of the references cited in paragraph 18 of the outstanding official action. Accordingly, this rejection is believed to be unsustainable and should be withdrawn for the reasons set forth below which were discussed with the Examiner.

Initially, Bednar (*Neurol. Res.*, 1996) has an effective date subsequent to Applicants' priority date. Accordingly, this reference is not available as prior art against the



present application and any rejection relying on this reference is believed to be unsustainable and should be withdrawn.

In general, the references cited in paragraph 18 of the official action, considered alone or in combination, do not suggest the present invention because the disclosures of these references do not suggest the efficacy of an anti-CD18 antibody for increasing cerebral blood flow or reducing infarct size in the absence of removal of the arterial obstruction. In fact, the references are representative of the common view in the art of a distinction between the efficacy of anti-CD18 antibodies in the treatment of ischemia/reperfusion injury vs. efficacy in no reperfusion ischemia. The references suggest that one should not see an increase in cerebral blood flow or a reduction of infarct size with non-reperfusion occlusion. This is directly contrary to the surprising results obtained by the method of the present invention. The specific and combined teachings of the references are addressed in more detail below.

Mori et al. (1992) conducted experiments to determine the effect of an anti-CD18 antibody on microvascular reflow after focal cerebral ischemia and reperfusion. Page 715, left column, first sentence in the Discussion. More specifically, Mori et al. "demonstrate an abrogation of this type of no-reflow by blockade of the principle PMN leukocyte adherence complex, CD11b/CD18." Page 715, left column, 5 lines from the bottom. Mori et al. further note that the antibody treatment was initiated immediately before reperfusion after occlusion. Page 717, last paragraph. The entire discussion in Mori et al., therefore, is directed to the effect of antibodies in a reperfusion injury, an injury which by definition involves removal of the arterial obstruction. Since the method of the present invention is directed to treatment of an injury in the absence of the arterial obstruction, studies of reperfusion injury are not relevant to the method of the present invention. 

Lindsberg et al. (1995) also discusses ischemia/reperfusion injury. Page 269, left column, first paragraph. The experiments described by Lindsberg et al. on page 269, right column, last paragraph over to page 270 describe prior experiments involving ischemia/reperfusion. The specific experiments described in Lindsberg et al. (1995) also involved an ischemia/reperfusion protocol. Page 270, right column. In the Discussion beginning on page 272, Lindsberg et al. indicate that the present study supports earlier observations regarding ischemia/reperfusion injury. Significantly, Lindsberg et al. note, on

page 275, a study by Clark et al. that an anti-CD18 antibody was effective in an ischemia/reperfusion model, but ineffective in a model of non-reperfusion. Lindsberg et al. also recognize the distinction between ischemia/reperfusion injury and non-reperfusion obstruction injury. These studies of Lindsberg et al. are directed only to ischemia/reperfusion injury. The comment by Lindsberg et al. regarding the Clark et al. experiments would lead one having ordinary skill in this art to believe that anti-CD18 antibodies are "ineffective" in models of non-reperfusion injury. This is a teaching directly away from the present invention.

Clark et al. (1991) referred to by Lindsberg et al. is of record in the present application. Clark et al. conducted an experiment in which 1 mg/kg of anti-CD18 antibody was administered to rabbits 30 minutes before inducing irreversible ischemia in the brain of the animal with intraarterial microspheres or in the spinal chord of the animal using reversible aortic occlusion. In the initial Discussion beginning on page 880, Clark et al. conclude that a significant effect of antibody treatment is seen in reperfusion, but not in non-reperfusion occlusion. Page 880, right column, last paragraph. See also page 882, left column, last paragraph. This suggestion is directly contrary to the surprising results obtained by the present invention.

Two additional references support the disclosure of Clark et al. See Garcia et al. (1996) and Chopp (Stroke abstract) both of record in this application. Garcia et al. studied the effects of an anti-CD11b/CD18 antibody on rats with permanent middle cerebral artery occlusion. After neuropathological evaluations, Garcia et al. conclude on page 247, left column, 3rd full paragraph:

Our experiments leave unanswered the question whether PMN leukocytes respond to or are one of the causes of neuronal necrosis. But, they reveal that a single injection of a MAb anti-CD11b/18 does not protect from the effects of permanent MCA occlusion of up to 4 days duration. (emphasis added)

Chopp et al. also find that anti-CD11b antibodies reduce infarction size only in transient ischemia, not in permanent focal ischemia in rats. See entire abstract.

Bednar (1992) also leads away from the present invention. Bednar et al. administered 1 mg/kg of antibody after delivery of an autologous blood clot to the anterior cerebral circulation. Bednar et al. summarized their findings stating in the abstract:

No statistically significant difference between the IB4 and control group was noted in cerebral blood flow (H_2 clearance technique) and infarct size (triphenyltetrazoliumchloride staining).

Bednar (1992), therefore, is consistent with the references discussed above.

Kim et al. (1995) and Lee et al. (1995) are both directed to ischemia/reperfusion injury. See Lee et al., page 460, left paragraph which describes the ischemia/reperfusion procedure and Kim et al., page 46 which describes treating patients with acute ischemic stroke and transient ischemic attacks (TIA). Lee et al. in the Discussion on page 463 present a hypothesis which they indicate is supported by observations that anti-CD18 antibodies are protective in reperfusion injuries. Page 463, right column, last full paragraph. Kim et al. in the discussion beginning on page 48, right column, indicate that CD18 is significantly upregulated only in the transient ischemic attack group. The combined disclosures of Kim and Lee, therefore, also lead one having ordinary skill in this art away from the present invention.

Hildreth (1989) and Hildreth (WO 9015076) disclose anti-CD18 antibodies and suggest use of these antibodies to treat an immune response mediated disorder (Hildreth WO 9015076, page 15). These references do not suggest the present invention and do not contradict or present contrasting evidence to the references discussed above. The Hildreth et al. references, therefore, are consistent with the combined disclosures of the previous references.

In summary, the combined disclosures of the references cited by the Examiner suggest a distinction between ischemia/reperfusion injury and occlusive injury without removing the obstruction. While efficacy is noted with reperfusion injury, the references clearly suggest no efficacy for occlusive injury in the absence of removing the obstruction. The results achieved by the present method are clearly surprising and not expected from the combined disclosures of the prior art. The claimed invention is, therefore, believed to be fully patentable over the disclosure of these references.

In view of the amendments and remarks made above, the claims now pending in this application are believed to be in condition for allowance. Early notice to this effect is earnestly solicited.

Serial No. 08/788,800

Page 8

Respectfully submitted,

GENENTECH, INC.

Date: August 24, 1998

By: 

Timothy R. Schwartz, Ph.D.

Reg. No. 32,171

1 DNA Way

So. San Francisco, CA 94080-4990

Phone: (650) 225-7467

Fax: (650) 952-9881